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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,454	12/08/2003	Arne Agerlin Olsen	5676.210-US	3283

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,454	OLSEN ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-34* is/are pending in the application.

4a) Of the above claim(s) *29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/417,608.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/8/06;12/8/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-21 have been cancelled;

Claims 22-34 are currently pending;

Claims 29-34 have been withdrawn;

Claims 22-28 are being examined in this application.

Election/Restrictions

1. Applicant's election of Group I (Claims 22-28 with SEQ ID NO. 88) in the reply filed on 9/5/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 29-34 and SEQ ID Nos (64 and 89-99) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/5/06.

3. Applicant's election without traverse of the following species:

A. the immunogenicity of the protein variant is below 75% of the immunogenicity of the parent protein;

B. the host cell is a bacterium;

C. the protein is an enzyme.

in the reply filed on 9/5/2006 is acknowledged.

Priority

4. This application appears to be a CONTINUATION of U.S. Patent Application Nos. 09/417,608 (filed 10/13/1999), which is now a US PATENT, 6,686,164 (2/3/2004). The '164 patent claims benefit of the following provisionals:

60/157,429 (10/04/1999)

60/114,386 (12/08/1998)

60/107,165 (11/05/1998).

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 60/114,386 and 60/107,165, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Both of the provisional applications ('386 and '165) do not disclose the specific "epitope pattern" of RYPR (SEQ ID NO 88) and RYPK, as recited in the instant Claim 27.

Thus, the priority date for the subject matter claimed in the instant Claim 27 is 10/04/1999.

6. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/417,608, filed on 10/13/1999.

Information Disclosure Statement

7. Applicants filed IDS (8/8/06 and 12/8/03) are considered and placed in the file. See the attached signed IDS forms.

Specification

8. The disclosure is objected to because of the following informalities: The instant disclosure recites lists of sequences in the drawings, which are not identified by their corresponding SEQ ID Nos in the "BRIEF DESCRIPTION OF THE FIGURES AND TABLES" of the instant specification. Applicants are requested to amend the instant specification and claims accordingly.

Appropriate correction is required.

9. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

11. Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite a protein variant having reduced immunogenicity as compared with its wild-type protein, wherein the amino acid sequence of the protein variant differs from the amino acid sequence of the parent protein with respect to at least one epitope area of the parent protein, such that the immunogenicity of the protein variant is below 75% of the immunogenicity of the parent protein.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

Claims 22-28 are drawn to a genus of protein variants that have certain reductions in immunogenicity. Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of "protein variants". In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genus of genes and genus of precursor molecules.

The claimed protein variant seems to have two characterisitics:

1.) The genus of protein variants has the common property of less than 75% or 50% immunogenicity of the parent.

2.) The genus of protein variants has amino acid sequence in at least one of the epitope area that is different from the parent protein's epitope area.

In regard to the first characteristic, the instant specification discloses "the term a protein variant having reduced immunogenicity as compared with the parent protein is meant a protein variant which differs from the parent protein in one or more amino acids whereby the immunogenicity of the variant is reduced" (p. 5, lines 20+). First, the instant specification does not disclose a common core structure and/or representative numbers of species for the "parent protein" that have certain immunogenicity. Although the instant specification lists numbers of proteins (p. 20+), the disclosure does not demonstrate these diverse proteins have a common core structure, and/or specific "immunogenicity".

In addition, the property immunogenicity of the "parent protein" from which the structures of the claimed genus of protein variants depend is also not adequately described to provide a structural limitation for the claimed "protein variants". That is the % reduction in

immunogenicity does not dictate a core amino acid sequence structure for the protein variants. From the definition cited above, the amino acid sequence of the protein variants can be any amino acid sequences that are different from the parent protein.

With respect to the second characteristic of the claimed protein variant, the instant specification only discloses examples of "parent proteins" that have different epitopes having different amino acid sequences (e.g. p. 46+). These different epitopes do not share a common structure (e.g. core amino acid sequences) even for the same parent protein. For example, the parent protein, "laccase", (p. 46), has 8 different sequences that do not share a common core sequence structure. One of ordinary skill in the art would not be able to describe the "protein variants" of the "parent protein", laccase that has reduced immunogenicity based on the sequence described in the instant specification.

The state of the art also does not provide guidance on the core structures for any "protein variant" of any parent protein that have different immunogenicity. The art does not show that one of ordinary skill in the art can reliably predict the immunogenicity of a protein (or protein variant) based on its structure and/or amino acid sequence. On the other hand, the art does teach changes in amino acids of a protein and its immunogenicity is highly unpredictable. For example, Lazoura et al (Current Medicinal Chemistry. Vol. 12: 629-639; 2005), review the designing of peptides (proteins) based vaccine for immunotherapeutic applications. The reference states that the immunogenicity of protein can be altered by modifying the amino acid sequences, however, the task is highly unpredictably and minor changes in peptide sequence can alter/abolish the immune response (or immunogenicity) (Abstract of the reference). Thus, it is

highly unpredictable to generate a protein variant that has different amino acid sequence from the parent and a certain % of immunogenicity.

The instant Claim 27 appears to recite additional structural limitation for the claimed protein variant by stating that "the epitope areas are defined on the wild-type protein structure by being localized less than 5 Angstroms from an of the following epitope patterns: RYPR/K (SEQ ID No: 88)". The SEQ ID No 88 recites only the sequence "RYPR", which is purported to be part of the PD498 protease protein as disclosed in the instant specification (p. 50, Table 2; p. 47, Table 1). A search of the GenBank database (See attached searched result from GenBank Accession Number AAB49694 (Bacillus PD498 Protease); downloaded 11/2/06), which indicates that the PD498 protease has 397 amino acids residues. The PD498 protease does not have the sequence recited in SEQ ID No 88. Furthermore, a sequence with only 4 amino acid residues does not constitute a core structure within a sequence of 397 amino acid residues. Thus, a "protein variant" based on the characteristics provided in the instant claim and specification would be highly unpredictable.

In addition, the recitation of "less than 5 Angstroms from" the RYPR (SEQ ID No88) does not offer structural limitation to the claimed protein variant. The instant specification discloses that the "5 angstroms" distance is predicted based on computer modeling of the parent or the variant protein (p. 52, lines 10+). However, it is known in the art that prediction of protein 3-D structure based on the primary amino acid sequence is highly unpredictable. For example, Xu et al (Current protein and Peptide. Vol. 1: 1-21; 2000) teach computational tools for protein modeling (Abstract of the reference). Xu et al teach that there are problems associated with protein modeling for predicting protein folding: different modeling tools can produce variation in

the predicted models; most predictions would require further experimental verification (p. 16, left-right col., bridging para); prediction based on sequence homology does not always yield similar function (p. 2, top of right col.); and alteration of sequences in the modeling region cannot usually be modeled reliably (p. 12, last para). Thus, it is highly unpredictable to generate protein folding models that would reliably predict the distance and locations of all the amino acid residues in a given protein. Without such reliable prediction, the protein variant based on the parent protein cannot be generated.

Therefore, the recited genus of protein variants is generated based on a trial and error process that would involve identifying the parent protein, identifying the epitope region, and identify parent protein folding structure. Without identifying the required protein, its structure and sequence that can be used to establish the protein variants, the claimed protein variant with the desired immunogenicity cannot be generated.

Therefore, applicants are not in possession of the genus of protein variants. Applicant's claimed scope represents only an invitation to experiment regarding possible proteins that might be generated to have the desired sequence and property.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Scope of Enablement Rejection

12. Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using protein variants based on Savinase listed on pp. 54-58 of the instant specification, does not reasonably provide enablement for making and using for protein variants that are based on other parent proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims/The nature of the invention

The breadth of the claims encompasses a genus of protein variants that have certain reductions in immunogenicity. Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of "protein variants". In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genus of genes and genus of precursor molecules.

The claimed protein variant seems to have two characterisitics:

1.) The genus of protein variants has the common property of less than 75% or 50% immunogenicity of the parent.

2.) The genus of protein variants has amino acid sequence in at least one of the epitope area that is different from the parent protein's epitope area.

In regard to the first characteristic, the instant specification discloses "the term a protein variant having reduced immunogenicity as compared with the parent protein is meant a protein variant which differs from the parent protein in one or more amino acids whereby the immunogenicity of the variant is reduced" (p. 5, lines 20+). First, the instant specification does not disclose a common core structure and/or representative numbers of species for the "parent protein" that have certain immunogenicity. Although the instant specification lists numbers of proteins (p. 20+), the disclosure does not demonstrate these diverse proteins have a common core structure, and/or specific "immunogenicity".

In addition, the property immunogenicity of the "parent protein" from which the structures of the claimed genus of protein variants depend is also not adequately described to provide a structural limitation for the claimed "protein variants". That is the % reduction in immunogenicity does not dictate a core amino acid sequence structure for the protein variants. From the definition cited above, the amino acid sequence of the protein variants can be any amino acid sequences that are different from the parent protein.

With respect to the second characteristic of the claimed protein variant, the instant specification only discloses examples of "parent proteins" that have different epitopes having different amino acid sequences (e.g. p. 46+). These different epitopes do not share a common

structure (e.g. core amino acid sequences) even for the same parent protein. For example, the parent protein, "laccase", (p. 46 of the instant spec.), has 8 different sequences that do not share a common core sequence structure. One of ordinary skill in the art would not be able to describe the "protein variants" of the "parent protein", laccase that has reduced immunogenicity based on the sequence described in the instant specification.

The state of the prior art/ The predictability or lack thereof in the art

The state of the art also does not provide guidance on the core structures for any "protein variant" of any parent protein that have different immunogenicity. The art does not show that one of ordinary skill in the art can reliably predict the immunogenicity of a protein (or protein variant) based on its structure and/or amino acid sequence. On the other hand, the art does teach changes in amino acids of a protein and its immunogenicity is highly unpredictable. For example, Lazoura et al (Current Medicinal Chemistry. Vol. 12: 629-639; 2005), review the designing of peptides (proteins) based vaccine for immunotherapeutic applications. The reference states that the immunogenicity of protein can be altered by modifying the amino acid sequences, however, the task is highly unpredictably and minor changes in peptide sequence can alter/abolish the immune response (or immunogenicity) (Abstract of the reference). Thus, it is highly unpredictable to generate a protein variant that has different amino acid sequence from the parent and a certain % of immunogenicity.

The instant Claim 27 appears to recite additional structural limitation for the claimed protein variant by stating that "the epitope areas are defined on the wild-type protein structure by being localized less than 5 Angstroms from an of the following epitope patterns: RYPR/K (SEQ

ID No: 88)". The SEQ ID No 88 recites only the sequence "RYPR", which is purported to be part of the PD498 protease protein as disclosed in the instant specification (p. 50, Table 2; p. 47, Table 1). A search of the GenBank database (See attached searched result from GenBank Accession Number AAB49694 (Bacillus PD498 Protease); downloaded 11/2/06), which indicates that the PD498 protease has 397 amino acids residues. The PD498 protease does not have the sequence recited in SEQ ID No 88. Furthermore, a sequence with only 4 amino acid residues does not constitute a core structure within a sequence of 397 amino acid residues. Thus, a "protein variant" based on the characteristics provided in the instant claim and specification would be highly unpredictable.

In addition, the recitation of "less than 5 Angstroms from" the RYPR (SEQ ID No88) does not offer structural limitation to the claimed protein variant. The instant specification discloses that the "5 angstroms" distance is predicted based on computer modeling of the parent or the variant protein (p. 52, lines 10+). However, it is known in the art that prediction of protein 3-D structure based on the primary amino acid sequence is highly unpredictable. For example, Xu et al (Current protein and Peptide. Vol. 1: 1-21; 2000) teach computational tools for protein modeling (Abstract of the reference). Xu et al teach that there are problems associated with protein modeling for predicting protein folding: different modeling tools can produce variation in the predicted models; most predictions would require further experimental verification (p. 16, left-right col., bridging para); prediction based on sequence homology does not always yield similar function (p. 2, top of right col.); and alteration of sequences in the modeling region cannot usually be modeled reliably (p. 12, last para). Thus, it is highly unpredictable to generate protein folding models that would reliably predict the distance and locations of all the amino acid

residues in a given protein. Without such reliable prediction, the protein variant based on the parent protein cannot be generated.

The above discussion only illustrated a few problems with making protein variants based on protein structure prediction (epitope areas localized less than 5 Angstroms from the epitope pattern) and property changes (reduction in immungenicity). Although there may be suggested methods of overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any parent proteins and their protein variants.

The level of one of ordinary skill

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction or guidance present/The presence or absence of working examples

The instant specification only discloses examples of "parent proteins" that have different epitopes having different amino acid sequences (e.g. p. 46+). These different epitopes do not share a common structure (e.g. core amino acid sequences) even for the same parent protein. For example, the parent protein, "laccase", (p. 46), has 8 different sequences that do not share a common core sequence structure. The instant specification discloses a working example of protein variants generated based on the parent protein, Savinase (p. 54+), however, other protein variants based on other parent proteins cannot be reliably generated based on the disclosure of the instant specification and the teaching of the art, because of generating protein variants with the desired structures and properties based on epitope pattern is highly unpredictable as

discussed above (under the heading "*The state of the prior art/ The predictability or lack thereof in the art*').

The quantity of experimentation needed

Due to the unpredictabilities of making protein variants based on protein structure prediction (epitope areas localized less than 5 Angstroms from the epitope pattern) and property changes (reduction in immungenicity), undue experimentation would be required. The art has not demonstrated all the possible protein variants that can be made based on all possible parent proteins. The art has not demonstrated any protein structure can be predicted based on amino acid sequences (such as epitope sequences). In addition, the art has also not demonstrated the feasibility of generating any protein variant that has the desired immunogenicity based on protein structure prediction. Thus, undue experimentation would be required for a person of ordinary skill in the art to make the claimed genus of protein variants in its full scope.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 22-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites the limitation "the parent protein" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "the epitope pattern" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 25 recites the limitation "the epitope" in line 25. There is insufficient antecedent basis for this limitation in the claim. The instant specification discloses that the terms "epitope" and "epitope area" are referring to different entities. For example, in Figure 1 of the instant disclosure, both the epitope and the epitope areas within the epitope are shown (p. 5, lines 5+).

Claim 27 recites the sequence "RYPR/K" followed by SEQ ID No: 88, which is unclear. The SEQ ID No. 88 as recited in the submitted Sequence Listing and in the instant specification (p. 50, Table 2) is referring to the sequence "RYPR", and does not refer to the sequence "RYPK". It is not clear as to which epitope sequence the instant Claim 27 is limited.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 22-26 and 28 are rejected under **35 U.S.C. 102(b)** as being anticipated by Lovborg et al (WO 92/10755; 6/25/1992; cited in IDS, filed 12/8/03).

The instant claims recite a protein variant having reduced immunogenicity as compared with its wild-type protein, wherein the amino acid sequence of the protein variant differs from the amino acid sequence of the parent protein with respect to at least one epitope area of the

parent protein, such that the immunogenicity of the protein variant is below 75% of the immunogenicity of the parent protein.

Lovborg et al, throughout the publication, teach methods of producing protein variants, and compositions of protein variants, that have reduced immunological response (reduced immunogenicity) (Abstract of the reference).

The reference teaches a protease variant, wherein the immunological potential has been changed in comparison to the parent protease (Claim 15 of the ref.), which reads on the protein variant having reduced immunogenicity as compared to the parent (or wild-type) protein of **clms 22 and 28**. The reference also teaches the protein variant has different amino acid sequence from the parent protein in the epitope (Claims 1 and 6 of the ref.), which reads on the amino acid sequence difference of **clms 22 and 28**.

The reference teaches certain protein variant has reduced immunoreactivity (immunogenicity) towards the antibodies generated against the parent protein, and the reduction can be below 75% or 50% of the parent immunogenicity (p. 8, lines 18+; pp. 10 & 12-14; Table II), which reads on the 50 and 75% reduction in immunogenicity of **clms 26, 22 and 28**, and the antibodies of **clm 23**.

The reference teaches the antibodies used to bind the protein variant are IgE antibodies (pp. 9-10, bridging para; Table II; p. 7), which reads on the IgE epitope pattern of **clm 24** because the IgE antibodies specifically recognized protein variants and their parent proteins.

The reference teaches various mutations in the epitope region of the parent protein (p. 16, Table III), which reads on the substitution and deletion of **clm 25** because the mutations in these regions changed the proteins' immunoreactivity against the specific antibodies.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 22-26 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-24, and 26-29 of copending Application No. 09/957806 (20050181446; 9/21/01). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '806 application claims a protein variant of a parent protein (Claim 22 of '806), and the protein variant has reduced immunogenicity of below 75% (Claim 29 of '806), which reads on the protein variant the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11/6/06

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